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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/826,463
Filing Date: April 05, 2001
Appellant(s): YAMAMOTO, NOBUTO

Joseph F. Murphy
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/29/2006 appealing from the Office action mailed 05/01/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal Number: 1999-1389.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,177,002	Yamamoto	1-1995
5,516,657	Murphy et al.	5-1996

5,652,352 Lichenstein et al. 7-1997

Cooke NE, David EV. Serum vitamin D-binding protein is a third member of the albumin and Alpha fetoprotein gene family. J Clin Invest. 1985 Dec;76(6):2420-4.

Luckow, V.A. "Protein Production and Processing From Baculovirus Expression Vectors," Chapter 4, In, Baculovirus Expression Systems and Biopesticides, editors, Michael L. Shuler et al. Publication date February 1, 1995. Pages 51-90.

Quirk et al. Production of recombinant human serum albumin from Saccharomyces cerevisiae. Biotechnol Appl Biochem. 1989 Jun;11(3):273-87.

Lu et al. Isolation and characterization of three recombinant human granulocyte colony stimulating factor His-->Gln isoforms produced in Escherichia coli. Protein Expr Purif. 1993 Oct;4(5):465-72.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the limitation "sequencing the cloned Gc1 isoform, thereby ... wild type Gc1 isoform;" (step (c) of claim 24) cannot be found in the originally filed disclosure, which raises the issue of new matter. This limitation lacks description in the originally filed disclosure, introduces a new concept, changes the meaning, scope and content of the original disclosure, and violates the description requirement of the first paragraph of 35 U.S.C. 112.

(10) Response to Argument

Appellant argues that the Specification as filed discloses that Appellant was able to determine, using chemically and proteolytically fragmented Gc, that the smallest domain, domain III contains an essential peptide for macrophage activation (Specification at page 10, lines 5-7); that furthermore, the Haddad reference (Haddad et al. 1992), which was cited in that paragraph and incorporated by reference in its entirety (Specification at page 28, lines 1-2), teaches that it was known in the art to sequence peptides of native serum Gc protein; that to be a proper incorporation by reference, it must be set forth in the specification and must: (1) express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) clearly identify the referenced patent, application, or publication (37 CFR 1.57); that here, the incorporation of the Haddad reference is shown by the use of that phrase, and the reference is clearly identified, thus the requirements of 37 CFR 1.57 are met.

Appellant submits that the relevant portion of Haddad which teaches sequencing of the Gc peptide (also known as DBP) is on p. 7175, column 2, ¶ 2:

> For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence in an Applied Biosystems 473A protein sequencer. The results obtained were compared with the known sequence of hDBP (Cooke & David, 1985).

that thus Haddad, incorporated entirely into the instant Specification, teaches the sequencing of Gc peptide (i.e., DBP) and comparison to known, wild-type (hDBP) protein; that the limitation in claim 24 subsection (c) is directed to sequencing of the Gc protein to determine whether it is wild-type; that this is exactly what the Haddad reference shows; that the fact that the protein source in Haddad is natural versus recombinant as in the present application is irrelevant; that the

Haddad reference teaches sequencing a Gc peptide and comparing it to wild-type, which is what the limitation covers.

Appellant argues that chemically (e.g., cyanogen bromide) and proteolytically (e.g., thrombin) fragmented Gcl protein yields overlapping peptides; that sequencing these peptides allows sequencing full-length Gcl protein; that these are the standard and well-established procedures for sequencing full-length proteins; that then, Appellant compares the full-length sequenced data of the cloned Gcl protein with the sequence of the full-length protein, as shown in Fig. 3, with known (or native known) Gcl peptide sequence (Cooke & David. J Clin Invest, 1985; 76:2420-24; also see Yamamoto '002); that the claim encompasses sequencing by fragments; that this limitation is thus not new matter because instead of repeating some information contained in another document, an application incorporates the content of another document or part thereof by reference to the document in the text of the specification; that the information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed; that replacing the identified material incorporated by reference with the actual text is not new matter.

Appellant's arguments have been fully considered but they are not persuasive. The relevant portion of the specification that refers to the Haddad reference is reproduced below:

> Domain I interacts with vitamin D while domain III interacts with actin (Haddad et al., Biochem., 31:7174, 1992). Chemically and proteolytically fragmented Gc enabled me to indicate that the smallest domain, domain III, contains an essential peptide for macrophage activation. Accordingly, I cloned both Gc protein and the entire domain III peptide, by the use of a baculovirus vector and an insect host, and treated them with the immobilized β-galactosidase and sialidase to yield potent macrophage activating factors, designated GcMAFc and CdMAF, respectively. Like GcMAF, these cloned GcMAFc and CdMAF appear to have curative effects on cancer.

Page 10, full paragraph 1. Firstly, this portion of the specification only refers to Haddad in regard to determining the functional domains of the Gc protein. Thus, it is not clear that appellant intended to incorporate by reference Haddad's sequencing procedure. Secondly, the specification indicates that appellant chemically and proteolytically fragmented Gc and determined that domain III contained an essential peptide for macrophage activation. However, the specification does not indicate that appellant sequenced either a portion of or the entire sequence of any chemical or proteolytic fragment of the Gc protein, assembled the entire Gc protein sequence from overlapping peptide sequences, and compared that sequence to a wild-type sequence. At best it might have been obvious to the skilled artisan that it would be desirable to determine the amino-terminal sequence of a chemical or proteolytic fragment of the Gc protein in order to determine the chemical or proteolytic cleavage sites, and hence the location of the fragment. However, the written description does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. It extends only to that which is disclosed. One shows that one "had possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. Thirdly, the specification indicates that appellant chemically and proteolytically fragmented Gc and determined that domain III contained an essential peptide for macrophage activation and then cloned both Gc protein and the entire domain III peptide, by the use of a baculovirus vector and an insect host. The specification does not indicate that appellant cloned Gc protein, by the use of a baculovirus vector and an insect host, and then chemically and proteolytically fragmented Gc, assembled the entire Gc protein sequence from overlapping peptide sequences, and compared

that sequence to a wild-type sequence. Therefore, the claim is not supported by the specification at page 10, full paragraph 1.

Regarding the material incorporated by reference, the following portion from Haddad seem most relevant for construing Haddad's DBP:

> Pure hDBP was isolated as previously described (Haddad et al, 1984) or purchased (Calbiochem).

Paragraph bridging pages 7174-7175. There is no evidence of record that Haddad's Gc protein was produced recombinantly. Appellants also acknowledge that Haddad's Gc protein was isolated from its native source and was not produced recombinantly (Appeal Brief, sentence bridging pages 5-6). Therefore, Haddad does not support the concept of cloning Gc protein by the use of a baculovirus vector and an insect host, then chemically and proteolytically fragmenting the cloned Gc, then assembling the entire Gc protein sequence from overlapping peptide sequences, and then comparing that sequence to a wild-type sequence

The following portions from the Haddad reference seem most relevant for construing Haddad's sequencing of hDBP:

> For peptides correlating with radioactivity in paired gel lanes, their stained membrane bands were isolated with a razor blade and were analyzed for amino-terminal sequence in an Applied Biosystems 473A protein sequencer. The results obtained were compared with the known sequence of hDBP (Cooke & David, 1985). Sequences for peptide fragments were then used to predict the likely enzyme cleavage site at the carboxy terminus of the identified peptide (Cooke & David, 1985).

Page 7175, right column, full paragraph 1.

> When a 50-kDa peptide from a trypsin digest was eluted from the native gel slice for size estimation by reducing SDS-PAGE, it was found also to exhibit specific binding of 25-OHD3. Therefore, the blotted peptide was analyzed for amino acid sequence at its amino terminus.

Page 7176, left column, full paragraph 1.

> Amino acid sequencing from the amino termini of the fragments revealed two peptides cleaved at Lys-35 and one at Arg-5. Page 7177, left column, full paragraph 1.
>
> Following transfer of Pro-Blott membranes from 20-cm, 15% polyacrylamide gels run under denaturing and reducing conditions, both peptides were sequenced (Table I, section B).

Page 7177, left column, last full paragraph. Table I (page 7178) shows the amino-terminal amino acid sequence of proteolytic fragments of hDBP. Although Haddad discloses *in vitro* transcription and translation of full-length and truncated rat DBP (page 7176, section bridging left and right columns), Haddad does not disclose sequencing of the translated product.

Therefore, Haddad only discloses determining the amino-terminal sequence of proteolytic fragments of the native, not recombinant or cloned, hDBP. This sequencing was done in order to determine the proteolytic cleavages sites. The sequencing was not done in order to confirm that the native hDBP is a wild type protein. Furthermore, the amino-terminal sequence of proteolytic fragments of the native hDBP would not confirm that the native hDBP is a wild type protein because the identity of the rest of the amino acid sequence of the native hDBP was unresolved. Therefore, Haddad cannot be fairly said to describe the concept of cloning a Gc1 isoform into a baculovirus vector and sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild type Gc1 protein.

In addition, neither the claims nor the specification indicate that the procedure in step (c) of claim 24, is limited to determining the N-terminal sequence of fragments of cloned Gc protein. Rather the claims encompass determining the entire sequence of the Gc protein, and comparing that sequence to the wild type sequence. Thus, the claim is not supported by Haddad because Haddad does not describe sequencing the entire Gc protein. The defect of claim 24 is

not whether peptide sequencing is a standard and well-established procedure or whether Haddad was properly incorporated by reference, but that claim 24 is to an invention neither disclosed nor suggested in the application.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems and Biopesticides, 1995 Feb:51-90).

Yamamoto teaches a process of converting glycosylated Gc protein (Gc1 isoform) to a highly potent macrophage activating factor (GcMAF) by contacting Gc protein with immobilized beta-galactosidase and sialidase (Example 2, columns 9-10; paragraph bridging columns 2-3; column 4, full paragraph 2; paragraph bridging columns 4-5).

The innermost sugar of the oligosaccharide moiety of Gc1 protein is N-acetylgalactosamine. Treatment of Gc1 protein with endo-N-acetylglucosaminidase, which results in the cleavage of the N-acetylgalactosamine, results in a molecule which cannot be then converted to macrophage activating factor (column 5, full paragraph 1).

The macrophage activating factor is believed to comprise a protein in substantially pure form having substantially the amino acid sequence of human Gc protein and a terminal O-linked N-acetylgalactosamine group (column 5, full paragraph 3).

The Gc protein is also known as "vitamin-D binding protein" (paragraph bridging columns 1-2). Yamamoto refers to Cooke (J Clin Invest. 1985 Dec;76(6):2420-4) for nucleotide and amino acid sequences of Gc protein (paragraph bridging columns 1-2). The Gc protein has a molecular weight of about 52,000, comprises approximately 458 amino acids, and has three distinct domains, as evidenced by Yamamoto (Figures 1 and 2) and Cooke (Figure 3; page 2423, paragraph bridging left and right columns).

Yamamoto purifies the Gc protein from human blood (column 5, full paragraph 5).

Yamamoto does not teach, only in the sense that Yamamoto does not anticipate, producing the Gc protein via recombinant DNA technology and converting the recombinantly produced Gc protein to GcMAF.

The concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology. See Quirk, page 273, last full paragraph. Material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity. See Quirk, paragraph bridging pages 273-274.

Cooke discloses a cDNA encoding the human vitamin D-binding protein (hDBP) and its nucleotide and amino acid sequence (page 2421, Figure 2). Comparison of the sequence of the hDBP mRNA and protein to existing protein and nucleic acid data banks demonstrates a strong and highly characteristic homology of the hDBP with human albumin (hALB) and human alpha-fetoprotein (hAFP). Based upon this structural comparison, Cooke establishes that DBP is a member of the ALB and AFP gene family. See the Abstract. Cooke's sequence represents the Gc1 allele (page 2424, left column).

Lichenstein discloses that the human serum proteins albumin (ALB), I-feta-protein (AFP) and vitamin D binding protein (VDB) are known to be members of a multigene ALB family. All three proteins are found in serum. See column 1, lines 10-15. Lichenstein discloses human afamin (AFM). It shares strong similarity to albumin family members and has the characteristic pattern of disulfide bonds observed in this family. In addition, the gene maps to chromosome 4 as do other members of the albumin gene family. Thus, AFM is the fourth member of the albumin family of proteins. AFM cDNA was stably transfected into Chinese hamster ovary cells and recombinant protein (rAFM) was purified from conditioned medium. See column 1, lines 45-65. Host cells from mammals, prokaryotes, fungi, yeast, insects and the like are used for the recombinant expression of AFM (column 13, lines 52-55).

Murphy provides Baculovirus vectors to express recombinant proteins during Baculovirus infection. One advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active. In addition, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems. Although mammalian expression systems result in the production of fully modified, functional protein, yields are often low. E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state. See column 1, lines 40-52. The list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors (column 6, full paragraph 3).

Luckow discloses that baculovirus vectors have become widely used to direct the expression of foreign genes. The recombinant proteins are antigenically, immunogenically, and

functionally similar to their authentic counterparts (page 51, full paragraph 1). Luckow discloses recombinant baculoviruses and baculovirus vectors (pages 55-66). Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full paragraphs 2-3). Expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (page 83, last full paragraph).

Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach producing Gc protein via recombinant DNA technology and its conversion to GcMAF.

However, it would have been obvious to one of ordinary skill in the art at the time of Appellant's invention to purify a Gc1 isoform from blood, contact the purified Gc1 isoform in vitro with immobilized beta-galactosidase and sialidase, and obtain GcMAF, as taught by Yamamoto, and to modify that teaching by (a) cloning a Gc1 isoform into a baculovirus vector; (b) expressing the cloned Gc isoform; (c) contacting the cloned Gc1 protein with immobilized β-galactosidase and sialidase; and (d) obtaining the cloned macrophage activating factor (GcMAFc), using the teachings of Cooke, Quirk, Lichenstein, Murphy, and Luckow, with a reasonable expectation of success.

One of ordinary skill in the art would be motivated to make this modification because the concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology, material derived from E. coli may present the problem of co-purification of LPS which has endotoxin activity, E. coli systems result in high yields of recombinant protein but the protein is not modified and may be difficult to purify in a nondenatured state, Gc protein (vitamin D binding protein) is a ALB family

member, host cells from insects can used for the recombinant expression of an ALB family member, foreign genes for human blood factors may be inserted into Baculovirus vectors, one advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active, Baculoviruses are not pathogenic to vertebrates or plants and do not employ transformed cells or transforming elements as do the mammalian expression systems, although mammalian expression systems result in the production of fully modified, functional protein, yields are often low, recombinant proteins expressed in baculovirus systems are antigenically, immunogenically, and functionally similar to their authentic counterparts, O-linked glycosylation is known to occur on foreign proteins expressed in insect cells, and expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems.

The invention is prima facie obvious over the prior art.

(10) Response to Argument

Appellant argues that:

> To establish a prima facie case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or combination) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP § 2143. To establish prima facie obviousness, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

Appellant argues that:

Here, the Examiner has not established a prima facie case of obviousness because the combined references do not teach or suggest all the limitations of the claim. The claim is drawn to a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, and contacting the cloned Gcl protein with immobilized beta-galactosidase and sialidase, thus obtaining the cloned macrophage activating factor (GcMAFc). In the '002 patent, Appellant purified native Gc isoform from human blood (plasma) and treated it with immobilized beta-galactosidase and sialidase to generate GcMAF. This is in contrast to the claimed method. The method disclosed in the '002 patent only generates GcMAF, not GcMAFc, as in the instantly claimed method. The patent does not teach or suggest cloning of Gcl, cloning Gcl in baculovirus vector, or contacting cloned Gc 1 with immobilized beta-galactosidase and sialidase. The protein disclosed in the '002 patent was not produced by cloning, but by affinity chromatography with human blood. This is an important distinction from the instantly claimed method since the native sequence of the Gcl protein is critical because when the major Gc isoform (Gcl) is produced in the baculovirus expression system, protein synthesis occasionally yields mutant Gc peptides having amino acid substitutions due to mistakes made during gene transcription and translation. However, Appellant does not use the cloned mutant peptides to produce GcMAFc because the mutant peptides are immunogenic in humans. Thus, only the cloned Gcl protein having the wild type peptide sequence (Figure 3 of the instant application) is used to generate GcMAFc. Thus, the cloned Gc protein has to be sequenced, and have the sequence as shown in Figure 3. Only methods of producing the wild type Gcl peptide synthesized via cloning can produce the GcMAFc, as in the instantly claimed method. Treatment of only the cloned Gc protein with immobilized beta-galactosidase and sialidase can generate GcMAFc. These deficiencies are not cured by Cooke. Cooke isolated cDNA and the Gc peptide sequence was deduced from the cDNA but never isolated Gc protein (even non-glycosylated Gc protein).

Appellant argues that:

The Examiner relies on Cooke to teach or suggest that the Gcl allele can be cloned. However, Cooke does not teach or suggest recombinant expression methods. The Examiner has cited Cooke (1985) for cloning Gc protein via E. coli. However, Cooke only cloned cDNA for Gcl protein and sequenced the cloned cDNA. The amino acid sequence of the entire Gcl protein was deduced from the cloned cDNA sequence (Figs. 2 and 3 of Cooke). Cooke never expressed Gc protein via the E. coli system, thus, Cooke never made the amino acid sequence of Gc protein. Also Cooke never studied the biological activity of the cloned Gc protein because they did not have it: "the primary amino acid sequence of DBP [i.e. Gc protein] was deduced only after DBP cDNAs were cloned and sequenced." (Cooke at 2422, legend to Figure 3, which shows the predicted amino acid sequence of hDBP). Since the Cooke reference teaches the use of prokaryotic

vector mediated cloning, any expressed protein would not be glycosylated. This Gc protein has never been used in in vivo biological studies. Thus the combination of the '002 patent and the Cooke reference does not teach or suggest a method of cloning Gcl in baculovirus vector, expression of a cloned Gcl protein in a baculovirus expression system, or contacting cloned Gcl expressed in a baculovirus system with immobilized beta-galactosidase and sialidase. These deficiencies are not cured by the '352 patent.

Appellant argues that:

The Examiner cites the '352 patent as allegedly showing or suggesting expression of several proteins including Gc protein in insect cells. However, the '352 patent discloses that human afamin, an albumin like protein, can be expressed in insect cells, not Gcl as in the instantly claimed method. The albumin protein family consists of four serum proteins, albumin, ct-fetoprotein, afamin, and vitamin D-binding protein (Gc protein). While they have three structurally similar domains, there are important differences between the family members. The molecular weight of three proteins (i.e., albumin, a-fetoprotein, and afamin) are approximately 87 kDa whereas Gc protein has a smaller molecular weight of 52 kDa. This is because Domain III of Gc protein has a large deletion (equivalent to only 43% of domain III of other albumin family proteins) and thereby the O-glycosylating site (420 threonine residue of Domain III) of the Gc peptide is available for glycosylation. Appellant teaches that Gc protein is the only O-glycosylated albumin family protein. Gc protein is a membrane-like protein as to O-glycosylation, but is as soluble as a serum protein. O-glycosylation usually occurs in membrane proteins and not in serum proteins. The O-glycosylation of a protein increases solubility and stability of the cloned protein. Since Gc protein is very different from other albumin family proteins, and given the importance of the differences, there is no teaching or suggestion in the '352 patent of the expression and isolation of any and all albumin like proteins, and no teaching or suggestion regarding the specific expression and isolation of Gcl protein in particular. In contrast, the '352 patent only discloses the expression of afamin in insect cells. Thus, the combination of the '002 patent, the Cooke reference, and the '352 patent does not teach or suggest a method of cloning Gcl in baculovirus vector, expression of a cloned Gcl protein in a baculovirus expression system, or contacting cloned Gc 1 expressed in a baculovirus system with immobilized beta-galactosidase and sialidase. These deficiencies are not cured by the Quirk reference.

Appellant argues that:

While the Quirk reference is directed to producing human serum albumin, it is silent with regard to Gc protein. Quirk et al. cloned and expressed human serum albumin in yeast. Although albumin and Gc protein are in the same family of serum proteins, albumin is a non-glycosylated protein, and differs from Gcl, as set forth above. There is no teaching or suggestion in the Quirk reference regarding the specific expression and isolation of Gcl protein in particular. Thus the combination of the '002 patent, the Cooke reference, the '352 patent, and the Quirk reference does not teach or suggest a method of

> cloning Gc 1 in baculovirus vector, expression of a cloned Gcl protein in a baculovirus expression system, or contacting cloned Gcl expressed in a baculovirus system with immobilized beta-galactosidase and sialidase. These deficiencies are not cured by the '657 Murphy patent and the Luckow reference.

Appellant's arguments have been fully considered but they are not persuasive. In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Despite the differences between Gc protein and other albumin protein family proteins, appellant acknowledges that "the O-glycosylating site (420 threonine residue of Domain III) of the Gc peptide is available for glycosylation." Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full paragraphs 2-3). The reasonable expectation is that the Gc protein would be O-glycosylated in insect cells. In summary, appellant's hypothetical regarding the differences between Gc protein and other albumin protein family proteins and the speculative importance of these differences does not correspond to the evidence of record in this case regarding the reasonable expectations of one of ordinary skill in the art..

Appellant argues that:

> With regard to the recombinant expression of Gcl in baculovirus, the Examiner relies on the '657 Murphy patent and the Luckow reference, and cites the supposed advantage of baculovirus in the expression of recombinant proteins. However, the only protein that Murphy expressed with this method is the HIV glycoprotein gpl20. Unlike the Gc protein, gpl20 is not sialylated. There is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of protein. The Examiner does not show how or where Luckow teaches or suggests that a baculovirus vector could be successfully employed to express Gc protein in insect cells. In addition, "[t]here are three possible sources for a motivation to combine references: the nature of the problem

> to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01. In the Final Office Action the Examiner admits that the motivation did not come from the prior art references (Final Office Action at 3), thus the motivation must come from the nature of the problem to be solved and the knowledge of persons of ordinary skill in the art. Here, the Examiner argues that the motivation comes from concern about human viral contamination if Gc is purified from human blood, and that these contaminants may be avoided if these products are obtained via recombinant DNA technology. The Examiner finds further motivation in the alleged advantages of the baculovirus expression system.

Appellant's arguments have been fully considered but they are not persuasive. There is no evidence of record to suggest that a sialylated protein could not be generated as easily as the HIV glycoprotein gpl20. Luckow discloses that baculovirus vectors have become widely used to direct the expression of foreign genes. The recombinant proteins are antigenically, immunogenically, and functionally similar to their authentic counterparts (page 51, full paragraph 1). Luckow discloses that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (page 74, full paragraphs 2-3). Expression of foreign genes by baculovirus vectors is an enabling technology that permits the production of proteins that cannot often be achieved with other expression systems (Luckow, page 83, last full paragraph). In summary, Appellant's hypothetical regarding the difficulty in producing a sialylated protein does not correspond to the record in this case teaching the advantages and popularity of baculovirus vectors, the fact that the recombinant proteins are antigenically, immunogenically, and functionally similar to their authentic counterpart, and the fact that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells.

Appellant argues that:

However, "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." W.L.Gore & Assocs., Inc. v. Garlock, Inc., 220 USPQ 303, 312-13 (Fed. Cir. 1983). Here, the prior art references do not teach or suggest all the, limitations of the claims, and thus the Examiner has used hindsight reasoning in constructing the rejection. Additionally, "[s]kill in the art does not act as a bridge over gaps in the substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process." All-Site Corp. v. VSI International Inc., 50 USPQ 1161, 1171 (Fed. Cir. 1999). The Examiner is attempting to substitute skill in the art to act as a bridge over the deficiencies of the teachings of the cited references, since the references themselves do not teach or suggest all the limitations of the claims.

Appellant argues that:

It is the Examiner's position that the combination of the references makes it obvious to practice a method of cloning Gcl in baculovirus vector, expression of a cloned Gcl protein in a baculovirus expression system, and contacting cloned Gcl expressed in a baculovirus system with immobilized beta-galactosidase and sialidase. The Examiner's position reflects the "obviousness to try" approach of the "armchair" chemist. Ex parte Maizel, 27 U.S.P.Q.2d 1662 (Bd.Pat.App & Interf.) (1992). In Maizel, the Examiner's rejection of claims for recombinant human B-cell growth factor as obvious in view of prior art, which examiner asserted described protein whose existence would have motivated one skilled in art to isolate protein, sequence it, construct synthetic DNA probes, utilize probes to isolate messenger RNA, synthesize cDNA, and produce additional protein, reflects "obviousness to try" approach of "armchair" chemist, and was reversed. The Board held that the protocol set forth by the examiner would not have been enabling to one of skill in the art. As in Maizel, here there is nothing in the references which teaches or suggests the expression of a properly glycosylated recombinant protein, or that a baculovirus vector could be successfully employed to express Gc protein in insect cells, and as in Maizel, here the protocol set forth by the Examiner would not have been enabling to one of skill in the art.

Appellant's arguments have been fully considered but they are not persuasive. As noted by appellant, the board in Ex parte Maizel held that the protocol set forth by the examiner would not have been enabling to one of skill in the art. However, in the present case there is no evidence that the cited references would not have enabled one of ordinary skill in the art to (a) clone a Gcl isoform into a baculovirus vector; (b) express the cloned Gcl isoform, thereby producing a

cloned Gcl protein; (c) contact the cloned Gcl protein with immobilized beta galactosidase and sialidase; and (d) obtain the cloned macrophage activating factor (GcMAFc). Therefore, appellants "obviousness to try" approach of the "armchair" chemist argument does not stand.

In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the appellant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellant argues that:

> The Examiner is focusing on the obviousness of substitutions and differences instead of on the invention as a whole, see Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). In the Hybritech case it was found that an immunometric assay which differed from the prior art by employing monoclonal antibodies bound to a solid carrier (i.e. a so-called sandwich) was patentable despite predictions of the utility of monoclonal antibodies and the fact that sandwich assays were known for polyclonal antibodies. The evidence showed that when monoclonal sandwich assay kits were introduced those skilled in the art were skeptical about their reliability so that their success was not reasonably expected by those skilled in the art. In Hybritech, the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. (Id. at 1383). Here, the attempt by the Examiner to substitute the baculovirus expression system for isolation of Gc protein from blood by affinity chromatography, when there is nothing in the references which teaches or suggests the expression of a properly glycosylated recombinant protein produced in the baculovirus expression system, or that a baculovirus vector could be successfully employed to express Gc protein in insect cells, is improper.

Appellant's arguments have been fully considered but they are not persuasive. The following teachings from the cited references seem most relevant for construing the teaching or suggestion to express a glycosylated recombinant protein in the baculovirus expression system:

> One advantage of the Baculovirus vectors over bacterial and yeast expression vectors includes the expression of recombinant proteins that are essentially authentic and are antigenically and/or biologically active. Murphy, column 1, lines 40-52.
>
> The list of foreign genes that may be inserted into the Baculovirus vectors includes human blood factors. Murphy, column 6, full paragraph 3.
>
> The Gc protein is a human blood factor. Yamamoto, column 5, full paragraph 5.
>
> The concern about human viral contamination in products purified from blood may be avoided if these products are obtained via recombinant DNA technology. Quirk, page 273, last full paragraph.
>
> Baculovirus vectors have become widely used to direct the expression of foreign genes. The recombinant proteins are antigenically, immunogenically, and functionally similar to their authentic counterparts. Luckow, page 51, full paragraph 1.
>
> O-linked glycosylation is known to occur on foreign proteins expressed in insect cells. Luckow, page 74, full paragraphs 2-3.

The examiner believes that substitution of the baculovirus expression system for isolation of Gc protein from blood by affinity chromatography is proper.

The examiner also takes issue with appellant's use of the term "properly glycosylated recombinant protein" to cast doubt on the reasonable expectation of one of ordinary skill in the art because GcMAFc is itself not a properly glycosylated protein in the sense that it has been treated with β-galactosidase and sialidase to remove most of the carbohydrate. According to Yamamoto:

> The innermost sugar of the oligosaccharide moiety of Gc1 protein is N-acetylgalactosamine (Coppenhaver et al., Arch Biochem. Biophys. 226, 218-223, 1983). Treatment of Gc1 protein with endo-N-acetylglucosaminidase, which results in the cleavage of the N-acetylgalactosamine, results in a molecule which cannot be then converted to macrophage activating factor. Column 5, full paragraph 1.
>
> Without wishing to be bound by any theory, it is believed that the above glycosylation occurs at the specific protein portion of the Gc glycoprotein through a threonine residue occurring at amino acid position 420 (Gc1

> phenotype) or through a threonine residue occurring at neighboring amino acid position 418 (Gc2 phenotype), thus forming the O-glycosidic linkage GalNAcα (1→0)-Thr. Thus, without wishing to be bound by any theory, the novel macrophage activating factor is believed to comprise a protein in substantially pure form having substantially the amino acid sequence of human group specific component, and a terminal N-acetylgalactosamine group linked to an amino acid residue, most likely threonine 420 and/or 418. Column 5, full paragraph 3.

Therefore, GcMAFc appears to contain a single N-acetylgalactosamine residue linked to an amino acid residue, most likely threonine 420 and/or 418. There is no evidence of record that N-acetylgalactosamine does not get attached to the Gc protein expressed in baculovirus vector expression systems. The fact that O-linked glycosylation is known to occur on foreign proteins expressed in insect cells (Luckow, page 74, full paragraphs 2-3) suggests that N-acetylgalactosamine does get attached to the Gc protein expressed in baculovirus vector expression systems. There is no evidence of record that O-linked glycosylation of the Gc protein in baculovirus expression systems would begin with anything other than N-acetylgalactosamine. Despite potential "non-human" post translational processing of secreted proteins in baculovirus vector expression systems, there is no evidence of record that "non-human" glycosylation patterns could not be removed with β-galactosidase and sialidase to expose the N-acetylgalactosamine residue linked to threonine 420 and/or 418 in the Gc protein.

Appellant argues that:

> As set forth above, the Examiner relied on the '657 Murphy patent and the Luckow reference to show the supposed advantage of baculovirus in the expression of recombinant proteins. However, the only protein that Murphy expressed with this method is the HIV glycoprotein gpl20. Unlike the Gc protein, gpl20 is not sialylated. There is no evidence in Murphy to suggest that a sialylated protein could be generated as easily due to the nature of protein. The Examiner does not show how or where Luckow teaches or suggests that a baculovirus vector could be successfully employed to express Gcl protein in insect cells. In addition, Gc 1 is a secreted protein. Many secreted and membrane proteins produced in the baculovirus expression system frequently form insoluble

aggregates or are improperly processed. Furthermore, although post-translational processing in insect cells is more similar to mammalian cells than bacteria and yeast, it is not always identical and, for applications such as therapeutic proteins, this is critical. Improper secretory processing can be especially problematic at several days post-infection when the host cell's post-translational processing machinery has deteriorated. Therefore protein produced in the baculovirus expression system can be poorly processed and be produced as aggregates, and is prone to improper post-translational modifications. In addition, while baculovirus expression systems generally perform post-translational protein modifications similar to those of mammalian cells, leading to correct secretion and subunit assembly, some recombinant proteins are extensively degraded. Moreover, the vulnerabilities of engineered proteins to proteolytic degradation differ, and the proteolytic activities in different insect cell lines differ as well. The optimal conditions for each case require careful and time-consuming determination. Therefore, given the art recognized difficulties with the baculovirus expression systems, particularly in the production of secreted proteins and post-translationally modified proteins, such as Gc1, a person of ordinary skill in the art would not have been motivated to practice a method of converting Gcl protein into GcMAFc by contacting the Gc protein with β-GAL and sialidase, wherein the protein had been produced in a baculovirus system.

Appellant further argues that:

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048 (CCPA 1976), see also Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success). Here, while the Examiner alleges the advantages of the baculovirus expression system, there are distinct disadvantages to using the baculovirus expression system, because it is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, as Gc is, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gcl isoform into a baculovirus vector because there was not a reasonable expectation of success.

Appellant further argues that:

> In addition, "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 771 F.2d 1496 (Fed. Cir. 1985). Here, there are distinct disadvantages to using the baculovirus expression system, particularly in the case of a secreted and post-translationally modified protein wherein the baculovirus system is prone to misprocessing of such proteins, while Appellant has demonstrated that the baculovirus system unexpectedly produces functional and soluble GcMAFc (see Table 3).

Appellant's arguments have been fully considered but they are not persuasive. The examiner does not agree that given appellant's post-filing date art recognized difficulties with the baculovirus expression systems a person of ordinary skill in the art would not have been motivated to use baculovirus expression systems for the production of GcMAF. Appellant's post-filing date art acknowledges that the baculovirus expression vector system (BEVS) is one of the major recombinant DNA expression systems used today for the production of a wide variety of heterologous proteins. One of the major advantages of BEVS is that it can be used to produce relatively large quantities of post-translationally modified heterologous proteins used in a number of applications. See Ailor (Curr Opin Biotechnol. 1999 Apr;10(2):142-5), page 142, left column. Furthermore, and as noted by appellant, there are potential disadvantages to using any expression system. See also Lu, wherein it is taught that potential mistranslation may happen in the production of any recombinant protein (page 471, right column, full paragraph 1). Appellant's hypothetical regarding the lack of motivation of one of ordinary skill in the art to express of the Gc protein in BEVS and the unexpected results do not correspond to the record in this case teaching the advantages, popularity and successes of BEVSs.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto (U. S. Patent No. 5,177,002) in view of Cooke (J Clin Invest. 1985 Dec;76(6):2420-4), Quirk (Biotechnol Appl Biochem. 1989 Jun;11(3):273-87), Lichenstein (U. S. Patent No. 5,652,352), Murphy (U. S. Patent No. 5,516,657), and Luckow (Baculovirus Expression Systems and Biopesticides, 1995 Feb:51-90) as applied to claim 22 above, and further in view of Lu (Protein Expr Purif. 1993 Oct;4(5):465-72).

Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow teach a process for producing GcMAFc comprising (a) cloning a Gc1 isoform into a baculovirus vector; (b) expressing the cloned Gc1 isoform; (c) contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase; and (d) obtaining the cloned macrophage activating factor (GcMAFc), as discussed above. Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow do not teach sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild-type Gc1 protein.

Lu teaches that the potential mistranslation that may happen in the production of any recombinant protein should seriously be taken into consideration. Appropriate purification processes should be evaluated and implemented to eliminate the undesired minor variant forms. A combination of protein analytical techniques, as described, can ensure the quality of the final product. See page 471, right column, full paragraph 1. Lu describes the analytical technique of protein sequencing (Abstract; page 467, left column, full paragraph 3). Lu does not teach a process for producing GcMAFc comprising cloning a Gc1 isoform into a baculovirus vector,

expressing the cloned Gc1 isoform, contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase, and obtaining the GcMAFc.

However, it would have been obvious to one of ordinary skill in the art at the time of Appellant's invention to (a) clone a Gc1 isoform into a baculovirus vector; (b) express the cloned Gc1 isoform; (c) contact the expressed Gc1 isoform with immobilized β-galactosidase and sialidase; and (d) obtain the cloned macrophage activating factor (GcMAFc), as taught by Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow, and to modify that teaching by sequencing the cloned Gc1 peptide, thereby confirming that the cloned Gc1 protein is a cloned wild-type Gc1 protein, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because potential mistranslation may happen in the production of any recombinant protein and to ensure the quality of the final GcMAFc product.

The invention is prima facie obvious over the prior art.

(10) Response to Argument

Appellant argues that:

> The claims are drawn to a process for producing a cloned macrophage activating factor (GcMAFc) by cloning a Gcl isoform into a baculovirus vector, expressing the cloned Gcl isoform, contacting the cloned Gcl protein with immobilized β-galactosidase and sialidase, thus obtaining the cloned macrophage activating factor (GcMAFc), and further wherein the cloned protein is sequenced. The base references U.S. Patent No. 5,177,002 (Yamamoto), Cooke (1985), Quirk (1989), U.S. Patent No. 5,652,352 (Lichenstein), U.S. Patent No. 5,516,657 (Murphy), and Luckow (1995) have been discussed, supra. The combination of the '002 patent, the Cooke reference, the '352 patent, the Quirk reference, the '657 Murphy patent, and the Luckow reference does not teach or suggest a method of cloning Gcl in baculovirus vector, expression of a cloned Gc 1 protein in a baculovirus expression system, or contacting cloned Gc 1 expressed in a baculovirus system with immobilized beta-galactosidase and sialidase. Additionally, claim 24 is further drawn to sequencing the cloned Gcl protein, which is also not taught

or suggested in the combination of these references. These deficiencies are not cured by the Lu reference.

Appellant further argues that:

> The Lu reference teaches that to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). However, the Lu reference is silent with regard to cloning Gcl in baculovirus vector, contacting cloned Gcl with immobilized beta-galactosidase and sialidase, or sequencing Gcl protein expressed in insect cells. Since all the limitations of the claims are not taught or suggested by the references, the rejection under 35 USC 103(a) is improper.

Appellant's arguments have been fully considered but they are not persuasive. Yamamoto in view of Cooke, Quirk, Lichenstein, Murphy, and Luckow teach a process for producing GcMAFc comprising (a) cloning a Gc1 isoform into a baculovirus vector; (b) expressing the cloned Gc1 isoform; (c) contacting the expressed Gc1 isoform with immobilized β-galactosidase and sialidase; and (d) obtaining the cloned macrophage activating factor (GcMAFc), as discussed above. In response to appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Appellant argues that:

> In addition, as above, while the Examiner alleges the advantages of the baculovirus expression system there are distinct disadvantages to using the baculovirus expression system, particularly in the case of a secreted protein, e.g., Gcl, wherein the baculovirus system is prone to misprocessing of secreted proteins. Additionally, in the case of post-translationally modified proteins, e.g., Gcl, the baculovirus system degrades several days after infection, and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates. The references teach that the optimal conditions for expression of a protein in the baculovirus expression system require careful and time-consuming determination. Thus, given the teachings of the references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the

recombinant protein will be poorly processed and accumulate as aggregates, it would not have obvious to one of skill in the art the time the invention was made to practice a method of cloning a Gcl isoform into a baculovirus vector because there was no motivation to combine the references, and there was not a reasonable expectation of success. In addition, the Examiner has further cited the Lu reference. The Lu reference teaches that mistranslation may happen in the production of any recombinant protein, thus this reference weighs against the finding of obviousness. The Lu reference teaches that sequence error at the translational level occurs at a higher frequency (Lu at 47 l, column 2, first full paragraph) in bacterial expression systems. While the Lu reference teaches bacterial expression systems, the Examiner has cited the reference to stand for the proposition that recombinantly produced proteins should be tested by sequencing after production. This is yet another reason why one of ordinary skill in the art would not have been motivated to practice the claimed method at the time the invention was made, because of the inherent problems with recombinant production of proteins. This is particularly an issue with proteins, as in the protein produced in the instant invention, wherein the proper amino acid sequence and post-translational modifications are critical. Lu teaches that in order to insure high product quality and to evaluate the effectiveness of manufacturing process in removing contaminants and impurities, a series of analytical methods is required to carry out extensive biochemical characterizations and biological analyses of the final purified product (Lu at 465, column 2, first paragraph). Thus, given the teachings of the Ailor and Ho references that the baculovirus system is prone to misprocessing of secreted proteins and a large fraction of the recombinant protein will be poorly processed and accumulate as aggregates, and the further teachings of Lu, as cited by the Examiner, that production of proteins by recombinant DNA technology can lead to sequence errors at the translational level, and require a series of analytical methods to carry out extensive biochemical characterizations and biological analyses of the final purified product, the claims are patentable because there is not a motivation to combine the references, and further, there was not a reasonable expectation of success.

Appellant's arguments have been fully considered but they are not persuasive. Although there may be difficulties with the baculovirus expression vector system (BEVS), there are also disadvantages to using any expression system. See for example Lu, wherein it is taught that potential mistranslation may happen in the production of any recombinant protein (page 471, right column, full paragraph 1). However, there is a general recognition in the art that recombinant expression techniques enable the production of large quantities of protein products (Lu, page 465, paragraph bridging left and right columns). Appellants post-filing date art (Ailor) also acknowledges that the baculovirus expression vector system (BEVS) is one the major

recombinant DNA expression systems used today for the production of a wide variety of heterologous proteins. One of the major advantages of BEVS is that it can be used to produce relatively large quantities of post-translationally modified heterologous proteins used in a number of applications. See Ailor (Curr Opin Biotechnol. 1999 Apr;10(2):142-5), page 142, left column). Appellants post-filing date art of Ho (Biochem J. 2004 Sep 1;382(Pt 2):695-702) acknowledges that since its introduction in 1983, the BEVS (baculovirus expression vector system) has become one of the most popular protein expression systems used in industry and molecular biology laboratories. BEVSs have several advantages over other recombinant protein expression systems, including high protein yields, ease of use and safety. However, although BEVSs generally perform post-translational protein modifications similar to those of mammalian cells, leading to correct secretion and subunit assembly, some recombinant proteins are extensively degraded. See Ho, page 695, left column, first paragraph of introduction. Therefore, the examiner concludes that Appellant's hypothetical regarding the lack of motivation of one of ordinary skill in the art to express the Gc protein in BEVS does not correspond to the record in this case teaching the popularity and advantages of BEVSs, and the general knowledge in the art that recombinant expression techniques enable the production of large quantities of protein products.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

David Romeo, Primary Examiner
David Romeo

Conferees:

Brenda Brumback, SPE

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Related Proceeding(s) Appendix

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 24

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte NOBUTO YAMAMOTO

Appeal No. 1999-1389
Application No. 08/618,485

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and MILLS Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4, which are all the claims pending in the application.

Claims 1 and 2 are illustrative of the subject matter on appeal and are reproduced below:

1. A process for cloning vitamin D_3-binding protein (Gc protein) into baculovirus comprising the step of selecting and using a baculovirus vector to clone the vitamin D_3-binding protein (Gc protein).

2. A process for producing a cloned macrophage activating factor (GcMAFc) comprising contacting cloned vitamin D_3 binding protein in vitro with immobilized ß-galactosidase and sialidase and obtaining the cloned macrophage activating factor (GcMAFc).

Claims 3 and 4 differ from claims 1 and 2 only in that claim 3 is a process for cloning vitamin D_3-binding protein domain III, and claim 4 is a process for producing cloned macrophage activating factor CdMAF wherein cloned vitamin D_3-binding protein domain III is contacted with ß-galactosidase and sialidase.

The references relied upon by the examiner are:

Yamamoto 5,177,002 Jan. 5, 1993

Cooke et al. (Cooke), "Serum Vitamin D-binding Protein is a Third Member of the Albumin and α Fetoprotein Gene Family," J. Clin. Invest., Vol. 76, pp. 2420-2424 (1985)

Luckow, Protein Production and Processing from Baculovirus Expression Vectors, in Insect Cell Cultures: Biopesticide and Protein Production Shuler et al. eds., John Wiley and Sons pp. 1-38 (1993)

GROUND OF REJECTION

Claim 1-4 stand rejected under 35 U.S.C. § 103 as being unpatentable over Yamamoto in view of Luckow and Cooke.

We affirm the rejection under 35 U.S.C. § 103 of claims 1 and 2, and reverse the rejection of claims 3 and 4.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims, and to the respective positions articulated by the appellant and the examiner. We make reference to the examiner's Answer[1] for the examiner's reasoning in support of the rejection. We further reference appellant's Brief[2], and appellant's Reply Brief[3] for the appellant's arguments in favor of patentability.

CLAIM GROUPING:

Appellant presents (Brief, page 3) two claim groupings. Group I (claims 1 and 2) do not stand or fall together with Group II (claims 3 and 4).

THE REJECTIONS UNDER 35 U.S.C. § 103:

Initially, appellant argues (Brief, pages 3-4) that the examiner cited the wrong Yamamoto reference in his statement of the rejection. Appellant argues (Brief, page 4) that "the rejection must be withdrawn (and properly restated in another Office Action, if desired), as it does not show how the cited references combine to make a prima facie case of obviousness." Appellant's arguments have been considered and are not persuasive. Appellant not only had notice of the correct Yamamoto reference (Brief, page 5, "the intended combination of references including Yamamoto (BB)...."), but responded to the examiner's position (Brief, pages 4-10) with reference to the correct Yamamoto reference.

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[1] Paper No. 21, mailed September 1, 1998.
[2] Paper No. 20, received June 24, 1998.
[3] Paper No. 22, received October 30, 1998.

In our opinion, given that appellant had notice of the typographical error in the Yamamoto reference designation and responded to the examiner's rejection in view of the correct Yamamoto reference, we find that the typographical error on behalf of the examiner did not prejudice appellant's case. According we find the do not Final Rejection fatally flawed by the examiner's typographical error. Therefore, we move forward to the merits of the examiner's rejection.

According to the examiner (Answer, page 3) Yamamoto disclose "a process of converting glycosylated Gc protein obtained from pooled blood to a highly potent macrophage activating factor (GcMAF) by contacting Gc protein with immobilized ß-galactosidase and sialidase." The examiner explains (Answer, page 4) that Yamamoto discloses "that Gc protein is also known as vitamin D-binding protein and that the nucleotide and amino acid sequences of Gc protein [including domain III] was reported by Cooke." The examiner relies on Luckow (Answer, page 4) to teach "a process for the abundant expression of exogenous proteins in insect cells using baculovirus expression vectors."

The examiner concludes (pages 5-6) that:

> One of ordinary skill in the art would be motivated to combine these teachings because cloning Gc protein in a baculovirus vector facilitates the abundant and economical expression of a glycosylated Gc protein that is antigenically, immunogenically, and functionally similar to its counter part isolated from natural sources on a scale that is not technically or economically feasible with other expression systems, and because the cloned Gc protein could be converted to GcMAF, a highly potent macrophage activating factor, which has utility as a therapeutic agent for inducing macrophage activation, as taught by Yamamoto et al. ...
>
> Furthermore, it would have been obvious to one of ordinary skill in the art at the time of Appellant's invention to clone the cDNA encoding domain III of the Gc protein, as taught by Cooke et al., into a

> baculovirus vector, as taught by Luckow, and to express the cloned domain III of the Gc protein in insect cells, as taught by Luckow, as recited in claim 3, with a reasonable expectation of success. Furthermore, it would have been obvious to one of ordinary skill in the art at the time of Appellant's invention to contact the recombinantly expressed domain III of the Gc protein in vitro with immobilized ß-galactosidase and sialidase, as taught by Yamamoto, as recited in claim 4, with a reasonable expectation of success.

Claims 1 and 2:

Appellant argues (Brief, page 6) that "the Office fails to show how or where Luckow teaches that baculovirus could be successfully employed to express vitamin D binding protein (i.e., Gc protein) in insects." Appellant argues (Brief, page 7) that Luckow "acknowledges the unpredictability of foreign protein expression by baculovirus vectors" because Luckow recognize "differences in the microheterogeneity of oligosaccharide structures are often observed for mammalian glycoproteins expressed in different mammalian cell lines or by individual cell lines under different culture conditions." In response to appellant's arguments the examiner argues (Answer, page 7) that "Luckow teaches at the paragraph bridging pages 15-16 that many baculovirus-expressed glycoproteins retain full biologic activity in in vitro assays, which would create a reasonable expectation of successfully using baculovirus vectors and insect cells for the abundant and economical expression of a glycosylated Gc protein."

With reference to Ausubel[4], appellant argues (Brief, page 8) that "one skilled in the art would not have had any such expectation of abundant, economical and

[4] Expression of Protein in Insect Cells Using Baculoviral Vectors, in Current Protocols in Molecular Biology, 6.8.1-6.11.7 (Ausubel et al., eds., Greene Publishing and Wiley-Interscience, New York 1990).

effective expression of Gc protein because 'the ability of a given recombinant virus to produce large quantities of foreign proteins must be determined empirically.'" We note however, that appellant's three quotations from Ausubel span 25 pages. Within those 25 pages, Ausubel also discusses the popularity of the baculovirus system, in addition to a number of advantages in using the system, e.g., "[o]ne of the beauties of this expression system is a visual screen allowing recombinant viruses to be distinguished [16.8.3]."

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In meeting this initial burden of establishing a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). As set forth in In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 "[o]bviousness does not require absolute predictability of success ... [f]or obviousness under § 103, all that is required is a reasonable expectation of success" [citations omitted].

In our judgment, on these facts, we find that the examiner met his burden of establishing that a person of ordinary skill in the art would have had a reasonable expectation of success in cloning vitamin D_3-binding protein into baculovirus comprising the step of selecting and using a baculovirus vector, and in producing macrophage activating factor comprising using the cloned vitamin D_3 binding protein in the method disclosed by Yamamoto.

Accordingly, we affirm the rejection of claims 1 and 2 under 35 U.S.C. § 103 as being unpatentable over Yamamoto in view of Luckow and Cooke.

Claims 3 and 4:

Appellant argues (Brief, page 9) that "[a]lone or in combination, none of the applied references disclose that domain III is responsible for the macrophage activating function of the protein, or that domain III could be independently cloned while preserving its structural and functional integrity."

In response, the examiner emphasizes, inter alia, that Cooke teach domain III of the vitamin D_3 binding protein. However, to establish a prima facie case of obviousness, there must be both some suggestion or motivation to modify the references or combine reference teachings and a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). On this record, the examiner fails to identify a suggestion in the prior art to specifically clone domain III of the vitamin D_3-binding protein. The examiner also fails to identify a suggestion to combine domain III of vitamin D_3 binding protein with immobilized ß-galactosidase and sialidase to obtain macrophage activating factor. Furthermore, the examiner fails to explain how the applied combination of references would provide one with a reasonable expectation of success that the combination of domain III of vitamin D_3 with ß-galactosidase and sialidase would result in obtaining macrophage activating factor.

Accordingly, we reverse the rejection of claim 3 and 4 under 35 U.S.C. § 103 as being unpatentable over Yamamoto in view of Luckow and Cooke.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED - IN - PART

William F. Smith Administrative Patent Judge	))))) BOARD OF PATENT
Donald E. Adams Administrative Patent Judge	)) APPEALS AND)) INTERFERENCES
Demetra J. Mills Administrative Patent Judge	))

DA/dm

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